

SLEEP-DISORDERED BREATHING

Effects of Zolpidem CR on Sleep and Nocturnal Ventilation in Patients with Heart Failure

Rodrigo C. Gatti¹; Patrick R. Burke, MD¹; Leonardo J. Otuyama¹; Dirceu R. Almeida, MD, PhD²; Sergio Tufik, MD, PhD¹; Dalva Poyares, MD, PhD¹¹Department of Psychobiology, Sleep Division, Universidade Federal de São Paulo, Brazil; ²Department of Medicine, Cardiology Division, Universidade Federal de São Paulo, Brazil**Study Objective:** This study aimed to evaluate the effects of zolpidem CR (controlled release) on sleep and nocturnal ventilation in patients with congestive heart failure, a population at risk for insomnia and poor sleep quality.**Methods:** Fifteen patients with heart failure (ischemic cardiomyopathy) and ejection fraction $\leq 45\%$ in NYHA functional class I or II were evaluated with full polysomnography in a placebo-controlled, double-blind, randomized trial. Patients underwent three tests: (1) baseline polysomnography and, after randomization, (2) a new test with zolpidem CR 12.5 mg or placebo, and after 1 week, (3) a new polysomnography, crossing the "medication" used.**Results:** A 16% increase in total sleep time was found with the use of zolpidem CR and an increase in stage 3 NREM sleep (slow wave sleep). The apnea hypopnea index (AHI) did not change with zolpidem CR even after controlling for supine position; however, a slight but significant decrease was observed in lowest oxygen saturation compared with baseline and placebo conditions (83.60 ± 5.51 ; 84.43 ± 3.80 ; 80.71 ± 5.18 , $P = 0.002$).**Conclusion:** Zolpidem CR improved sleep structure in patients with heart failure, did not change apnea hypopnea index, but slightly decreased lowest oxygen saturation.**Keywords:** heart failure, polysomnography, zolpidem CR, sleep**Citation:** Gatti RC, Burke PR, Otuyama LJ, Almeida DR, Tufik S, Poyares D. Effects of zolpidem CR on sleep and nocturnal ventilation in patients with heart failure. *SLEEP* 2016;39(8):1501–1505.**Significance**

Sleep disorders are common in patients with heart failure (HF). Caution is recommended when prescribing sedative-hypnotic drugs in this population, they may cause depression of ventilation. Given the high prevalence of HF and insomnia; the deleterious nature of this association; the need of treatment alternatives to improve sleep; and the low potential of zolpidem to cause respiratory depression, we report data from our randomized, placebo-controlled, crossover trial, showing that a single dose of zolpidem CR was safe, improved sleep, did not change RDI, but caused a slight but significant decrease in lowest SpO_2 in a homogeneous sample of HF patients. Despite zolpidem CR having an acute safe profile, its long-term effect in HF patients who complain of insomnia deserves further study.

INTRODUCTION

Cardiovascular diseases are the most prevalent chronic diseases in the world¹ and result in heart failure (HF) symptoms,² associated comorbidities, and poor quality of life.

Sleep disorders are common in HF patients, with approximately 75% of patients reporting poor sleep. Among these disorders, insomnia and sleep apnea⁴ are the most common.⁴ Insomnia occurs in 25% to 56% of patients with HF,⁵ and sleep apnea occurs in 47% to 83% of cases, as they have common pathophysiological processes, such as increased sympathetic activation and increased sodium and water retention.⁶ In addition, insomnia is associated with an increased risk for cardiovascular disease possibly mediated by hypertension or elevated resting heart rate,⁷ which could negatively affect HF patients' clinical outcomes.

In many of these patients, HF itself, associated with sleep disturbances, leads to nocturnal sleep disruption and consequent poor sleep quality, exacerbating heart condition symptoms.⁸ Eventually, this clinical picture, associated with complaints of insomnia and/or excessive daytime sleepiness, makes these patients seek medical help to try to circumvent the problem.⁹

Among the most commonly prescribed hypnotics are benzodiazepines; however, these drugs may present potential depressant effects on the ventilatory responses of elderly patients or in those for whom this response is already compromised; these types of medication may also result in addiction.¹⁰ In contrast to benzodiazepines, zolpidem is a non-benzodiazepine

GABA-A receptor agonist that has been widely prescribed to treat insomnia.¹¹ A recent review reported the results of 2 studies in severe obstructive sleep apnea patients using 10 to 20 mg of zolpidem. Compared with placebo, zolpidem did not worsen AHI; however, 20 mg reduced lowest oxygen saturation without changing the oxygen desaturation index.¹² Since sleep-disordered breathing, either obstructive and central, and insomnia are prevalent among HF patients,^{3–6,8} and no studies have evaluated the effect of non-benzodiazepine GABA-A receptor agonists on breathing during sleep in patients with HF of ischemic etiology, we sought to evaluate the effects of zolpidem on sleep and nocturnal ventilation in this group. Our hypothesis is that zolpidem CR improves polysomnographic nocturnal sleep parameters in patients with New York Heart Association (NYHA) Class I or II HF.

METHODS**Population**

A total of 15 consecutive patients aged over 30 were evaluated. They were recruited from the outpatient clinic of the São Paulo Cardiomyopathy Division, São Paulo Hospital, Universidade Federal de São Paulo, after clinical and laboratory evaluations and diagnosis of ischemic cardiomyopathy and ejection fraction $\leq 45\%$ in NYHA functional class I or II. Patients who had regularly used benzodiazepines or other medication to induce sleep in the previous month were excluded. In addition, we excluded patients with laboratory test changes suggestive

Table 1—Demographic and anthropometric data (n = 15).

Age (years)	59.13 ± 7.60
Weight (kg)	67.89 ± 13.32
Height (m)	1.63 ± 0.10
BMI (kg/m ²)	25.54 ± 3.74
Night neck circumference (cm)	P = 0.068 { 38.23 ± 3.69
Morning neck circumference (cm)	
Abdominal circumference (cm)	95.93 ± 10.76
Hip circumference (cm)	94.33 ± 9.09
Waist/hip ratio	1.02 ± 0.06
ESS (score)	9.73 ± 5.15
PSQI (score)	9.13 ± 5.20
NYHA (class)	1.73 ± 0.97
British Council scale (score)	1.47 ± 1.30
Modified Borg scale (score)	1.93 ± 2.31

Values presented as mean ± standard deviation. ESS, Epworth sleepiness scale; PSQI, Pittsburgh sleep quality index; NYHA, functional class according to the New York Heart Association.

of liver and/or kidney failure. Therefore, plasma creatinine values ≥ 1.3 mg/dL led to exclusion from the protocol. Fifteen patients were included in the final sample. All patients were taking medication, including β -blockers, for treatment of their heart condition in accordance with the standard outpatient treatment protocol.

Sociodemographic data, such as body mass index (BMI), age, gender, and neck circumference, and echocardiographic data, such as the diameter of the heart cavities, cardiac mass index, and ejection fraction, were also evaluated.

Study Design

This study was a double-blind, randomized, placebo-controlled, crossover trial. Patients underwent baseline polysomnography and were randomized into two groups. A further polysomnogram was then performed after taking 12.5 mg zolpidem CR or placebo. After a further week, another polysomnogram was performed, switching the “medication” used on the second examination day. There was a washout period of one week between polysomnograms. Bedtime was stipulated preferably by the patient according to their routine and was evaluated using a sleep diary.

Polysomnography

Full polysomnography was performed at the Sleep Institute laboratory (AFIP, Sao Paulo, Brazil), Sleep Medicine Division, Psychobiology Department, (Universidade Federal de Sao Paulo, Brazil), at three points: the first evaluation was performed on the first test day (baseline), and the other two evaluations were performed with intervals of one week between them (treatment with zolpidem CR or placebo).

The overnight polysomnography was performed using an EMBLA digital system (17 channels, Medicare Medical Devices). The following variables were monitored: electroencephalogram (4 channels), electrooculogram (2 channels), electromyogram (2 channels: submental and anterior

tibialis muscles), electrocardiogram (one channel D2 modified), snoring, and body position. The airflow was monitored using a thermocouple and a nasal pressure transducer (Pro-Tech Services Inc., Mukilteo, Washington). Chest and abdominal piezo-sensors monitored the respiratory effort of each patient. Arterial oxygen saturation (SpO₂) and pulse were recorded using a pulse oximeter (Nonin, model 9500, Plymouth, USA). All of the polysomnograms were performed and scored by an experienced sleep technician who followed the American Academy of Sleep Medicine (AASM) guidelines for sleep studies¹³ and were reviewed by a sleep medicine physician.

Sleep Quality Questionnaires

On the first day of baseline polysomnography, patients completed the following questionnaires: the Epworth Sleepiness Scale (ESS)¹⁴, the Pittsburgh Sleep Quality Index (PSQI)¹⁵, the New York Heart Association Functional Classification (NYHAFC)¹⁶, dyspnea scales¹⁷, and the Modified Medical Research Council (MMRC) scale.¹⁸

Statistical Analysis

The software Statistica v12 (Statsoft, Tulsa, OK, USA) was used for data analysis. All demographic, anthropometric, echocardiographic, and polysomnographic data are presented as means ± standard deviations or frequencies. To compare the means of the polysomnographic data, analysis of variance (ANOVA) for repeated measures was used followed by the Bonferroni *a posteriori* test when needed. The significance level adopted was $P \leq 0.05$.

RESULTS

Demographic, Anthropometric, and Echocardiographic Evaluations

No adverse event was reported with zolpidem CR or placebo in this trial, with the exception of a mild morning headache episode in one patient.

The descriptive characteristics of the sample are presented in Table 1. Table 1 shows that the population studied presented borderline sleepiness score on the Epworth Sleepiness Scale (ESS), which was 9.73 ± 5.15 points (excessive sleepiness is considered when > 10). However, the population exhibited a score of 9.13 ± 5.20 on the Pittsburgh Sleep Quality Index (PSQI), suggesting poor sleep quality. Scores on the Medical Research Council scale, which measures dyspnea during exercise, of 1.47 ± 1.30 , and on the modified Borg scale of 1.93 ± 2.31 , indicate mild to moderate weariness, reinforcing the condition presented by our sample of 1.73 ± 0.97 on the NYHA functional class scale (data presented in Table 1).

Table 2 shows the echocardiographic parameters of the HF patients. As expected, they had low ejection fraction, left ventricular dilation, and reduced cardiac mass index, characterizing cardiac involvement.

Polysomnography

The patients' polysomnographic data obtained after the three tests are shown in Table 3. Significant differences can be observed in the N3 stage and TST, which increased with the use

of zolpidem CR ($P = 0.01$ for both). The other sleep architecture parameters did not differ between treatments. In relation to respiratory sleep parameters, no significant change was detected in the apnea-hypopnea index (AHI), the respiratory disturbance index (RDI), or the central or obstructive respiratory event index during REM sleep, NREM sleep, or sleep in the supine position between treatments. Minimum O_2 saturation was lower in the zolpidem CR group ($P = 0.002$); however, the percentage of time with oxygen saturation less than 90% and the mean saturation did not differ significantly between treatments.

DISCUSSION

This is the first study, to the best of our knowledge, assessing the acute effect of a non-benzodiazepine GABA-A receptor agonist, in this case zolpidem CR, in HF patients with reduced ejection fraction. Overall results suggest that zolpidem increased total sleep time and N3 NREM sleep compared with placebo and baseline. We did not find significant changes in

AHI and RDI, even after controlling for supine position. However, a slight but significant decrease in lowest SpO_2 was found with zolpidem compared with placebo and baseline conditions.

There have been a number of reports in the literature on HF patients suggesting that they have poor sleep quality as assessed by PSQI,^{19,20} and fragmented sleep for various reasons,

Table 2—Echocardiographic data (n = 15).

Aortic diameter (mm)	32 ± 3
LV diameter (mm)	40 ± 4
LV diastolic diameter (mm)	58 ± 6
IV septum thickness (mm)	9 ± 1
Mass index (g/m ²)	135 ± 31
LV ejection fraction (%)	32 ± 7

Values presented as mean ± standard deviation. LV, left ventricle; IV, interventricular.

Table 3—Comparison of polysomnographic data: baseline, placebo and zolpidem CR conditions (n = 15).

Variable	Baseline Mean	Placebo	Zolpidem CR	P value
Sleep latency (min)	29.05 ± 30.04	25.31 ± 44.97	17.19 ± 20.75	0.677
REM latency (min)	132.47 ± 82.45	116.18 ± 81.62	139.93 ± 88.62	0.540
TST (min)	324.70 ± 84.11	330.25 ± 78.04	383.29 ± 68.89*	0.017
SE (%)	71.91 ± 17.79	74.85 ± 17.93	82.84 ± 13.11	0.068
N1 (%)	17.08 ± 10.22	15.86 ± 12.24	13.71 ± 13.55	0.336
N2 (%)	46.41 ± 11.48	42.41 ± 10.83	44.02 ± 10.05	0.333
N3 (%)	20.44 ± 8.82	22.44 ± 10.93	27.11 ± 13.64*	0.015
REM (%)	16.11 ± 4.96	19.54 ± 7.26	15.16 ± 8.68	0.066
WASO (min)	97.37 ± 54.69	90.69 ± 77.41	62.36 ± 48.12	0.137
Arousals (events/h)	20.83 ± 7.46	19.89 ± 10.27	17.65 ± 12.28	0.453
Respiratory events (n)	139.27 ± 88.94	128.57 ± 81.57	145.14 ± 92.76	0.719
Obstructive apnea (events/h)	3.00 ± 4.34	3.71 ± 3.02	5.76 ± 4.92	0.174
Obstructive apnea REM (events/h)	2.66 ± 3.82	5.69 ± 7.78	9.96 ± 14.19	0.100
Obstructive apnea supine (events/h)	5.28 ± 9.78	8.41 ± 8.42	12.25 ± 13.90	0.377
Central apnea (events/h)	7.21 ± 13.14	9.89 ± 17.58	5.45 ± 13.97	0.626
Central apnea REM (events/h)	1.05 ± 1.59	4.26 ± 14.66	3.11 ± 11.46	0.669
Central apnea supine (events/h)	11.95 ± 19.15	12.85 ± 19.53	10.65 ± 16.29	0.739
RDI (events/h)	25.23 ± 15.52	24.44 ± 15.68	23.89 ± 17.62	0.817
AHI (events/h)	22.41 ± 16.44	22.81 ± 16.31	22.16 ± 17.72	0.938
AHI in REM (events/h)	17.58 ± 9.20	25.45 ± 19.38	24.91 ± 24.12	0.376
AHI supine (events/h)	42.22 ± 29.78	36.74 ± 19.74	39.94 ± 29.02	0.812
Apnea (events/h)	11.69 ± 14.66	14.42 ± 17.91	12.56 ± 15.26	0.830
Hypopnea (events/h)	10.71 ± 8.37	8.41 ± 4.77	9.60 ± 6.10	0.334
Time spent in supine position (%)	47.46 ± 32.75	50.79 ± 33.30	47.88 ± 33.13	0.878
SpO_2 baseline (%)	94.27 ± 1.71	94.29 ± 2.09	93.73 ± 2.33	0.336
SpO_2 mean (%)	93.41 ± 1.74	93.19 ± 2.29	92.45 ± 2.56	0.082
Lowest SpO_2 (%)	83.60 ± 5.51	84.43 ± 3.80	80.71 ± 5.18*	0.002
REM desaturation (events/h)	21.55 ± 16.02	22.48 ± 16.44	26.26 ± 27.42	0.747
NREM desaturation (events/h)	22.85 ± 20.60	20.66 ± 17.20	21.39 ± 17.13	0.718
$SpO_2 < 90$ (%)	7.33 ± 9.54	13.29 ± 22.43	18.86 ± 26.66	0.104

Values presented as mean ± standard deviation. ANOVA for repeated measures. * $P \leq 0.05$ zolpidem CR differs from baseline and placebo. TST, total sleep time; SE, sleep efficiency; WASO, wake after sleep onset; AHI, apnea hypopnea index; RDI, respiratory disturbance index.

such as sleep apnea and insomnia.^{4,5} Similarly, we found poor sleep quality using similar questionnaire, a mean baseline AHI of 22.41 ± 16.44 , and fragmented sleep as evidenced by increased WASO and arousal index in our population.

There is no consensus on the best sleep-inducing medication for patients with HF. As zolpidem is one of the most commonly prescribed hypnotics,²¹ and reported to be safe with few dose-dependent adverse events,²² in this study we decided to evaluate its effects in a homogeneous sample of patients with HF of ischemic origin, which, with hypertension, is the most common etiology of HF.²³ Patients did not report significant adverse events after a single dose of zolpidem CR, with the exception of a mild morning headache episode in one patient.

Unlike benzodiazepines, in healthy controls, zolpidem has little effect on sleep stages.²⁴ Zolpidem is as effective as benzodiazepines in decreasing sleep latency and prolonging TST in patients with insomnia.^{25,26} In fact, our study showed that in patients with ischemic HF, zolpidem CR prolongs TST by an average of 16% compared to placebo. We also observed a trend toward an increase in sleep efficiency compared with placebo ($P = 0.06$). As for sleep stages, there was a significant increase in N3 in the zolpidem CR group. The combination of increased TST and increased N3 stage (slow wave sleep) indicates an improvement in the sleep pattern, which in theory could be beneficial for patients with HF, since N3 is a sleep stage where cardiac demand is at its lowest for the day, as a lower heart rate, blood pressure, and respiratory rate are observed.²⁷ REM sleep, however, did not change significantly with the use of zolpidem CR. Together, these results suggest an improvement in sleep architecture in patients with HF acutely treated with zolpidem CR.

With regard to potential breathing effects, zolpidem has been reported as having fewer muscle-relaxant effects than benzodiazepine hypnotics, which has been mostly studied in animals.²⁸ In our study, zolpidem CR showed a slight but statistically significant reduction in lowest oxygen saturation. A previous study also showed similar results in severe OSA patients without HF; a slight reduction in lowest oxygen saturation with no changes in AHI with a higher than usual therapeutic dose, 20 mg of zolpidem.²⁹ Moreover, studies show that another GABA-A agonist, eszopiclone, may not change³⁰ or may even improve breathing patterns during sleep, especially for individuals whose sleep is highly fragmented, and thus for whom the ventilatory drive becomes unstable.³¹

However, some guidelines suggest that this drug should not be used in patients with respiratory depression.³² This effect could be attributed to an effect within the central chemoreflex loop at the central chemoreceptors,³³ which could actually reduce respiratory events in patients with HF and central sleep apnea. Zolpidem has been reported as devoid of muscle-relaxant effects, thus unlikely to affect oropharyngeal muscles²⁴; and does not cause respiratory depression in insomnia patients.²⁶ Similarly, our study revealed that in patients with ischemic HF, no significant increase in obstructive respiratory events, in overall AHI or RDI, or in OSA and CSA indices per hour were detected compared with placebo and baseline conditions. The only study, to the best of our knowledge, evaluating the long-term effects of zolpidem on sleep parameters in

patients with OSA treated with CPAP, reported an improvement in sleep latency and arousal index, without affecting AHI, ODI, and lowest SpO₂, compared with placebo.³⁴

Another issue to be considered when computing the number of obstructive or central apneas is the time spent in the supine position, which is known to possibly increase obstructive and even central events.³⁵ In our study, we also evaluated the respiratory disturbance indices during sleep in the supine position and found no differences.

Potential limitations of this study include the relatively small sample size, although other studies evaluating populations with sleep-disordered breathing and the use of sleep aids used similar or smaller samples including sample sizes calculation to detect a significant difference in AHI of 5 per hour.³⁴ In addition, we did not evaluate the duration of respiratory events but did control for supine position and type of events. Lastly, our data refer only to a single dose. Despite zolpidem CR having an acute safe profile, its long-term effect in HF patients who complain of insomnia deserves further study.

CONCLUSIONS

The hypnotic zolpidem CR improves sleep structure because it increases N3, a deep sleep phase, and TST. Zolpidem CR also tends to increase sleep efficiency, which can be beneficial for the cardiovascular system. Furthermore, zolpidem CR did not increase the overall rate of apneas and hypopneas and decreased lowest oxygen saturation without affecting respiratory events of central origin.

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